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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,743	08/25/2003	Keisuke Teshigawara	0020-5172P	1791

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/15/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/15/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/646,743	TESHIGAWARA ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction requirement received on 10/27/06 has been entered. Claims 1-14 are pending in the instant application. Applicant's election of Group II is acknowledged. As the applicant has not indicated that the election was made with traverse or provided any arguments traversing the restriction requirement, the election of Group II is considered to have been made without traverse. Thus, the restriction requirement is deemed proper and is made FINAL. Claims 1-2, and 10-13 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 3-9 and 14 are currently under examination. An action on the merits follows.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/868,779, hereafter the '779 application, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the specification of the '779 application fails to disclose culturing lymphocytes with a cell that expresses any immunoglobulin superfamily gene, or specifically CD40, LFA-1 or combinations of any of B7, CD40, or LFA-1. The disclosure of the '779 application is limited to the expression of B7 and does not teach or suggest the genus of immunoglobulin superfamily genes or CD40 or LFA-1 in particular. It is noted that none of the instant claims are limited to the solely limited to the expression of B7. Further, the '779 application fails to disclose obtaining NK cells from a healthy patient, activating the cells in vitro and readministering them to the patient who now has cancer. The '779 application only teaches the use of lymphocytes from patients who already have cancer and does not teach or suggest using NK cells from patients when they are healthy and then reserving the cells for use in later therapy. As such, none of the instant claims under consideration, claims 3-9 and 14, are entitled to benefit of priority to parent application 09/868,779 or to PCT/JP00/07835 upon which the 09/868,779 national stage application was based. Therefore, the effective filing date for claims 3-9 and 14 is the filing date of the instant application, 8/25/03.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figures 2, 3, 4A and 4B are so dark as to be illegible and/or undecipherable. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

Claim Objections

Claims 3 and 14 are objected to because of the following informalities: claims 3 and 14 include limitations which reference withdrawn claims 1-2 or 13. Appropriate correction is required. It is suggested that applicant amend claims 3 and 14 to delete reference to the withdrawn claims and to add the desired limitations from withdrawn claims 1-2 or 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-9 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of B7 transfected K562 cells to activate NK cells *ex vivo* to produce NK cells capable of treating cancer in a patient, does not reasonably provide enablement for methods of immunostimulation or treating cancer disease in a patient by activating NK cells *ex vivo* by contacting lymphocytes with any cancer cell which expresses any immunoglobulin superfamily genes that encodes a cell adhesion molecule. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims read broadly on the of any cancer cell which expresses any immunoglobulin superfamily gene encoding an adhesion molecule to activate NK cells present in a lymphocyte population *ex vivo*. The specification also broadly discloses the genus of immunoglobulin superfamily genes. However, aside from B7, CD40, and LFA-1, the specification does not identify specific immunoglobulin superfamily cell adhesion genes useful in the instant methods of activating NK cells capable of treating cancer. It is further noted that the working examples are limited to the use of K562 cells transfected with a plasmid encoding B7, and do not exemplify the ability of K562 cells or any other type of tumor cells transfected with CD40, LFA-1 or any other immunoglobulin superfamily gene member to activate NK cells in culture such that the NK cells could be effectively used to treat any type of cancer.

The working examples demonstrate that the culture of peripheral blood lymphocytes with K562 cells expressing recombinant B7 results in activated NK cells and killer T cells capable of killing cancer cells. The working examples further show that the NK cells activated using the instant methods with K562-B7 cells were tested in clinical trials with human patients and were shown to be effective in treating a number of different cancers in humans. Thus, the working examples demonstrate the ability of K562-B7 cells to activate NK cells which can be administered to treat cancer. However, the results obtained with K562-B7 cells are not correlative to the genus of immunoglobulin superfamily genes and cancer cells expressing the immunoglobulin superfamily genes as claimed. At the time of filing, the prior art teaches that the immunoglobulin superfamily of genes are genes whose protein products comprise an

immunoglobulin superfamily domain, which is based on an amino acid sequence capable of making an immunoglobulin fold. Barclay, however, teaches, that there the immunoglobulin superfamily in humans, for instance, contains at least 878 different genes, of which the majority are membrane proteins that interact with other membrane proteins, i.e. are cell adhesion molecule (Barclay (2003) Seminars in Immunology, Vol. 15, 215-223, see page 222). It is also noted that Barclay does not teach that CD40 is in fact an Ig superfamily member, see Figure 4 which does not show that CD40 contains and IgSF domain which are indicated by red ovals. Barclay further states that genes with IgSF domains are the second most common type of genes with common domains, behind only genes encoding zinc fingers domains, and that the domain itself has not specific enzymatic activity (Barclay, *supra*, page 222, Table 4). The presence of the common Ig fold domain in the family members does not impart any shared activity or function to the superfamily, and aside from sharing a structural domain, the immunoglobulin superfamily members include proteins with highly disparate functional properties and activities. Thus, based on the large number of genes present in the immunoglobulin superfamily, and the fact that the shared IgSF domain does not impart any particular shared functional activity to the family members, a nexus between the activity seen with B7 any other Ig superfamily members cannot be made. Thus, based on the nature of the Ig superfamily genes, the lack of particular guidance for family members useful in the instant invention other than B7, CD40, or LFA-1, of which CD40 does not even appear to be an Ig superfamily member, the breadth of the claims, and the limitation of the working examples to the use of B7, the skilled artisan would not have been able to predict without undue experimentation which of the hundreds of Ig superfamily members

other than B7 could be used to activate NK cells as claimed which could then be used to treat cancer.

In addition, the specification fails to provide an enabling disclosure for the use of any cancer cell expressing B7 to activate NK cells according to the instant methods. As noted above, the working examples are limited to the use of K562 cells. K562 cells are an established leukemic cell line which is MHC negative, lacking both MHC class I and II expression. At the time of filing, it was well known that NK cells tolerance versus activation is significantly effected by the presence and level of expression of MHC antigens on the surface of the target cell. Cabrera et al. teaches that the presence and level of expression of MHC antigens on cancer cells determine the degree of activation and killing capacity of NK cells by interacting with NK receptors. Any change in the MHC profile of tumor cells (including classical and nonclassical MHC molecules) may therefore have a profound influence on the immune recognition and immune rejection of cancer cells. (Cabrera et al. 92003) Canc. Immunol. Immunother., Vol. 52(1) 1-9, see page 1). While the instant application demonstrates that cancer cells lacking MHC molecules, K562 cells, are capable of activating NK cells, the specification fails to provide sufficient guidance as to other cancer cells which have the same activity as the K562 cells which completely lack expression of MHC molecules when transfected with B7. Cabrera et al. further teaches that cancer cells vary substantially in their MHC expression profile, from downregulated expression of MHC class I and/or class II to loss of specific haplotypes. The specification does not provide any guidance as to the level of MHC molecules present which can be present on cancer cells that would allow those cells to be used to activate NK cells according to the instant methods. Thus, based on the relationship between MHC antigen expression on cancer cells and

their ability to activate NK cells, the substantial diversity in MHC expression profiles in cancer cells, the lack of guidance provided in the specification for cancer cells other than K562 cells transfected with B7 which are capable of activating NK cells according to the instant invention, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the full scope of the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,261,839 B1 (2001), hereafter referred to as Multhoff et al. The applicant claims a process for activating NK cells that circulate in a subject comprising administering activated NK cells as prepared by a process of claim 1 or 2, and a method of treating cancer by administering activated NK cells according to claim 13 where the NK cells were obtained from a healthy patient.

Multhoff et al. teaches the treatment of cancer by administering NK cells, which have been activated ex vivo by increasing the lytic activity of the NK cells for target cells, to a subject having cancer (Multhoff et al., column 16, claims 19-20). Multhoff et al. further teaches that the NK cells can be derived from patients to be treated, i.e. patients with cancer, or healthy subjects,

and that the NK cells are reinfused into the subject after ex vivo activation (Multhoff et al., column 1-2, bridging paragraph, and columns 2-3).

While the ex vivo activation taught by Multhoff et al. differs from the ex vivo methods taught in the instant specification, the resulting NK cells derived from both the Multhoff et al. method and the applicant's method appear to be the same in structure and function. The instant processes/methods do not specifically recite as method steps any particular ex vivo method for making the NK cells to be administered. While the methods indicates that the NK cells to be administered were made using a particular process, this situation is analogous to a product by process claim. For product by process, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

Therefore, by teaching the exact same method steps as recited in the claims, Multhoff et al. anticipates the instant methods as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,261,839 B1 (2001), hereafter referred to as Multhoff et al. in view of Ichiyama Masahiko (2000) Karei Igaku Kenkjujo Zasshi, Vol. 51 (3/4), 93-110, English abstract. The applicant claims processes for immunostimulation in a cancer patient and methods for treating cancer in a patient comprising isolating lymphocytes, incubating the lymphocytes with a cancer cell which

expresses an immunoglobulin superfamily gene, and reintroducing the activated NK cells to the patient. The applicant further claims said processes and methods wherein the cancer cells are K562 cells, wherein the immunoglobulin superfamily gene is B7, and wherein the steps are repeated.

Multhoff et al. teaches the treatment of cancer by administering NK cells, which have been activated ex vivo by increasing the lytic activity of the NK cells for target cells, to a subject having cancer (Multhoff et al., column 16, claims 19-20). Multhoff et al. further teaches that the NK cells can be derived from patients to be treated, i.e. patients with cancer, or healthy subjects, and that the NK cells are reinfused into the subject after ex vivo activation (Multhoff et al., column 1-2, bridging paragraph, and columns 2-3). Multhoff et al. further teaches that the ex vivo method of activation includes isolating peripheral blood lymphocytes and culturing the lymphocytes comprising NK cells and K562 cells at a high temperature followed by culture at a lower temperature in the presence of an alkylphospholipid and IL-2 (Multhoff et al., columns 7-8). The resulting activated NK cells exhibit enhanced lysis of target cells and the ability to kill cancer cells and treat caner in vivo.

Multhoff et al. differs from the instant invention by not teaching that the K562 cells express an immunoglobulin superfamily gene that encodes a cell adhesion molecule, or more specifically B7. Ichiyama Masahiko supplements Multhoff et al. by teaching that the culture of peripheral blood lymphocytes with K562 cells transfected with genes encoding a tumor antigen and B7-1 enhanced lymphocyte proliferation and induced CD56 dominant effector cells (i.e. NK cells) that displayed strong cytotoxicity against both MUC1+ and MUC1- target tumor cells, and that this method can be used to generate non-HLA-restricted effector cells with strong

cytotoxicity (Ichiyama Masahiko, abstract). Thus, in view of the strong NK cell cytotoxicity induced by K562 cells expressing B7, it would have been *prima facie* obvious to the skilled artisan to utilize K562 cells expressing B7 in the ex vivo methods of Multhoff et al. in order to generate NK effector cells with stronger cytotoxicity against target tumor cells. Further, in view of the high level of skill in the art of molecular biology, the skilled artisan would have had a reasonable expectation of success in making K562 cells expressing B7 and using those cells in place of regular K562 cells in the methods of treating cancer taught by Multhoff et al.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER